REMARKS/ARGUMENTS

Status of the claims

As an initial matter, Applicants would like to thank the Examiner for withdrawing the restriction requirement and indicating the allowability of claim 10, if rewritten in independent form. Claims 1-18 and SEQ ID NOs: 1-9 are presently under examination. Claims 1, 3, 7, 13, 14, 15, and 17 have been amended for the purpose of providing improved clarity. Claim 16 has been canceled. Claim 19 has been added. No new matter has been added by the amendments and added claim. Support can be found in the claims as filed and throughout the specification, for example, at pages 14-15 and 19-20. No claim amendment should be construed as an acquiescence in any ground of rejection.

Rejection under 35 U.S.C. § 101

Claim 1 is rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. Although Applicants do not necessarily concur, at the suggestion of the Examiner, Applicants have amended claim 1 to include the term "synthetically". Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 14 and 16 are rejected under 35 U.S.C. § 101 as improper process claims. In response, claim 14 has been amended to include a process step and claim 16 has been canceled.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 1-9 and 11-18 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. To the extent that the rejection applies to the claims as amended, Applicants respectfully traverse because there is no evidence of record so much as suggesting that those skilled in the art would be unable to practice the claimed invention.

The enablement requirement of 35 U.S.C. § 112 mandates that the specification teach those skilled in the art how to make and use the claimed invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The test of enablement is **not** simply whether experimentation would have been necessary, but whether such experimentation would have been **undue**. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404. Any conclusion of non-enablement must be based on the evidence as a whole. *Id.*

The Examiner bears the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide reasonable expectation as to why scope of protection provided by claim is not adequately enabled by disclosure); MPEP §2164.04. A specification **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *Id.* at 224. As stated in the MPEP:

> [I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there

> would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d at 224, 169 USPQ at 370.

The present rejection does not satisfy this standard. In particular, the Action presents no art-supported substantiation of its assertions. Rather, it sets forth only a general assertion that a skilled practitioner would not know how to make and use the presently claimed conotoxin peptides. Conotoxin peptide chemistry, however, is well known, as are general methods of using conotoxin peptides. There is considerable structural similarity among the various classes of conotoxin peptides and the Action provides no reason to believe that the methodology described in the specification cannot be used with any class of conotoxin peptides or any individual conotoxin peptide. Conotoxin peptides have been known for many years and there is a vast amount of literature describing such peptides, methods for their preparation, as well as their use in therapy. Indeed, the Action's allegations regarding an allegedly low level of skill in the art are refuted even by the references it cites to support its other rejections. Both Olivera *et al.* (U.S. Patent No. 4,447,356) and Shon *et al.* (WO 96/33206), for example, provide guidance on how to synthesize conotoxin peptides and assess the activity of the newly-synthesized conotoxin peptides. Despite the vast amount of literature on conotoxin peptides, however, Applicants are not aware of any suggestion or motivation in the art to connect the N- and C- termini to form an amide cyclized version of such peptides.

The present invention relates, in part, to the discovery that the cyclization of the peptide backbone of conotoxin peptides, such as those conotoxin peptides described in the art, results in novel compounds that, in many instances, retain the therapeutic activity of the original non-amide cyclized peptides. The present inventors are believed to be the first to

realize the benefits that can be obtained by cyclizing the backbone of a conotoxin peptide by linking the N- and C- terminus of a conotoxin peptide. Prior to the present invention, it could not have been expected that conotoxin peptides should be cyclized in such a manner or that, in this cyclized form, they would retain therapeutic activity.

Methods of synthesizing "linear" conotoxins (non-amide cyclized conotoxins) are well known in the art. The specification, on page 3, points to several references that teach methods of synthesizing linear conotoxins. On pages 5-7 of the specification, methods of cyclizing known linear conotoxins are provided. On page 8 of the specification, a representative list of known linear conotoxins that can be cyclized using the methods of the preset invention is provided. Examples 1, 2, 5, and 6 of the specification provide detailed instruction on how to synthesize and cyclize conotoxins. A skilled practitioner, armed with the knowledge in the art, would thus be able to routinely cyclize known conotoxin peptides according to the methods of the present invention.

The Action's assertion of undue breadth appears to be based on an assumption that enablement requires an exemplification of all possible uses of the claimed invention, *e.g.*, in this case, the showing of an effective treatment of a disease using the claimed conotoxin peptides. Such a requirement, however, is not consistent with the patent laws. Using the conditions set forth in the claims, the teachings of the specification, and routine methodology, any competent technician would be able to synthesize a known "linear" conotoxin peptide, cyclize it according to the methods of the present invention, and determine the extent to which the cyclized peptide has retained the activity of its parent. The possibility that the cyclized peptide has activity but is not able to entirely remedy a disease state does not render the claims non-enabled. Furthermore, it is improper for the PTO to require any showing

regarding the degree of effectiveness of therapeutic inventions. According to MPEP § 2107.03, "[o]ffice personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials .... [I]t is improper for office personnel to request evidence...regarding the degree of effectiveness [in humans] (emphasis in the original)." Enablement requires only that the application teach how to make and use the invention without undue experimentation. *In re Sichert,* 566 F.2d 1154 (C.C.P.A. 1977).

Because the Action fails to identify any reason why a skilled practitioner, following the methods described in the present application, would not be able to cyclize known conotoxin peptides and determine their activity, *e.g.,* by binding assays, Applicants submit that claims 1-9 and 11-18 are sufficiently enabled. Accordingly, the rejection of the claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 3 and 7 are rejected as allegedly indefinite for use of the term "derivative thereof" and "derived from". Although Applicants do not necessarily concur, in order to expedite prosecution, Applicants have amended the claims to delete reference to the disputed terms. It will be understood that the term "conotoxin peptide" as recited in the claims encompasses those peptides that share structural similarity with naturally occurring conotoxin peptides and possess conotoxin activity.

Claim 13 is rejected as allegedly indefinite for use of the term "if required". Although Applicants do not necessarily concur, Applicants have amended the claims to delete reference to the disputed term.

Claims 14-16 are rejected as allegedly indefinite for not setting forth essential steps and for use of the terms "conditions or diseases". Although Applicants do not necessarily concur, claims 14 and 15 have been amended to delete reference to the disputed terms and to more clearly reflect the claimed invention. Claim 16 has been canceled. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1-4, 15 and 16 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Olivera, *et al.*(U.S. Patent No. 4,447,356); claims 1, 3, and 5 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Pallaghy, *et al.* (Protein Science 3, 1833-1839 (1994); and claims 1-5 and 14-16 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Shon, *et al.* (WO 96/33206). According to the Action, Olivera, *et al.* teaches cyclic conotoxin GI, Pallaghy, *et al.* teaches cyclic ω-conotoxin GVIA, and Shon, *et al.* teaches cyclic δ-conotoxin PVIA and cyclic μ-conotoxin PIIIA. To the extent that this rejection applies to the claims as amended, Applicants respectfully traverse because there are aspects of the claimed subject matter that the cited references neither disclose nor suggest.

For a rejection under § 102(b) to be properly founded, a single prior art reference must disclose, either expressly or inherently, each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

The present claims are directed to synthetically cyclized conotoxin peptides having *amide cyclized backbones* such that the conotoxin peptides have no free N- or C- termini. The rejection cites Olivera, *et al.,* Pallaghy, *et al.,* and Shon, *et al.* as the bases for the § 102(b) rejection yet fails to identify in any of the cited reference any disclosure of a synthetic cyclized conotoxin peptide having an amide cyclized backbone as recited in the present claims. In view of at least this missing element, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

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Leslie Aberman
Limited Recognition under 37 C.F.R.
§ 10.9(b) Attached

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